Exhibit C

Cangrelor AstraZeneca

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AstraZeneca is developing the P2T ($P2Y_{ADP}$) purinoceptor antagonist and platelet aggregation inhibitor, cangrelor, for the potential treatment of unstable angina and as an ultrafast-acting intravenous antithrombotic agent. It is in phase IIb clinical trials [315723]. NDA and MAA applications are planned for after 2003 [275466], [314472]. It superseded the earlier compound, ARL-67085, which also reached phase II trials [328760]. In ex vivo samples of angina patients' blood, cangrelor inhibits platelet/monocyte conjugate development, which indicate the drug has some degree of disease-modifying activity [377418].

AstraZeneca is also developing derivatives of cangrelor. Removal of the triphosphate side chain, modification of the ribose to a carbocycle and the purine to a triazolopyridine resulted in a potent (IC_{50} = 4 nM) orally-active P2T/$P2Y_{12}$ receptor antagonist. A lead compound was scheduled to enter trials as an antithrombotic agent in July 2000 [377666].

In March 1999, Lehman Brothers predicted a 30% probability that the drug would reach world markets and would be launched in 2002 [336599].

Originator AstraZeneca plc

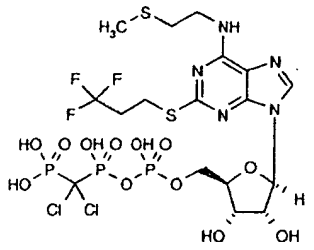
Status Phase II Clinical

Indication Angina, Thrombosis, Myocardial infarction

Action Purinoceptor modulator, Platelet aggregation inhibitor

Synonyms & Analogs AR-C69931, AR-C69931MX

CAS 5'-Adenylic acid, *N*-[2-(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-, monoanhydride with (dichloromethylene) bis[phosphonic acid]
Registry No: 163706-06-7



Introduction

Platelet adhesion and aggregation are pivotal events in normal hemostasis and arterial thrombosis, implicated in the pathogenesis of myocardial infarction, unstable angina and stroke [183665]. Many studies have contributed to an understanding of the mechanism of platelet aggregation and thrombus formation. Platelets respond to a variety of blood vessel injuries, such as narrowing of the lumen, plaque formation and the presence of foreign bodies (eg, catheters), leading to a sequence of events including platelet adherence and activation and the release of platelet granular components, including the potent cellular mitogenic factors. The activated platelet aggregates induce the formation of fibrin, which further stabilizes the thrombus. The platelet P2T receptor plays a major role in platelet aggregation, and antagonists to it are predicted to have significant therapeutic potential as antithrombotic agents [262006].

Human platelets possess three adenosine diphosphate (ADP) receptor subtypes: $P2Y_1$, P2T and $P2X_1$ [393812]. The P2T-purinoceptor is a member of the metabotropic P2Y-purinoceptor family that, together with inotropic P2X-purinoceptors, mediate the physiological actions of nucleoside polyphosphates [212999], [218491]. The P2T subtype, which has recently been redefined as a $P2Y_1$-purinoceptor, is largely confined to blood platelets, and its presence has also been detected on endothelial cells where it mediates vasodilation by ADP [262011]. ADP is present in high concentrations in dense granules of platelets and is released during platelet aggregation. It plays a key role in hemostatsis as it stimulates the platelet aggregation response induced by other agents [393808]. Adenosine 5'-triphosphate (ATP) is a competitive antagonist of the actions of ADP at the P2T-purinoceptor, but it is not acceptable as a therapeutic agent due to a lack of specificity and efficacy. Moreover, it is rapidly metabolized to ADP, which, in turn activates platelets [212999], [218491]. Structural manipulation of ATP, an antagonist of the platelet P2T receptor, led to the discovery of AR-C69931MX (cangrelor), a potent, selective and safe intravenous inhibitor of ADP-induced platelet aggregation [298982], [393813].

The first highly potent antagonist of the P2T receptor, AR-C67085, was > 1000-fold selective for this subtype. Further modification of the structure resulted in cangrelor with an IC_{50} value of 0.4 nM. *In vivo*, at maximally effective antithrombotic doses, there is little prolongation of bleeding time (1.4-fold), which is in marked contrast to the 5- to 6-fold prolongation observed with fibrinogen receptor (glycoprotein (GP) IIb/IIIa) antagonists. Cangrelor is 6-fold more potent than AR-C67085, but the compounds show a similar half-life (79% recovery of aggregation behavior after 20 min) [315723].

Synthesis and SAR

As a starting point for the discovery of useful antithrombotic agents, ATP presents a range of intriguing challenges, including physicochemical and biological lability of the polyphosphate moiety, low affinity for the P2T receptor (pIC_{50} = 3.6), lack of selectivity between P2 subtypes and extreme physicochemical properties [315723].

Cangrelor is an analog of ATP with a 3,3,3-trifluropropylthio substituent at C(2), an N^6-methylthioethyl substituent on the purine (adenine) base and a dichloromethylene group

replacing the β-γ linking oxygen in the acidic triphosphate chain. A series of weak P2T antagonists was prepared from adenosine monophosphate analogs [315723]. The triphosphate side chain was modified by replacing the anhydride oxygen with a dihalomethylene group to prevent hydrolysis to ADP and to enhance the receptor affinity, relative to unsubstituted methylene derivatives and substitution at C(8) of the adenine ring, which is reported to result in reduced affinity, whereas substitution at C(2) by thioalkyl or haloalkylthio groups enhanced affinity and was optimal with a thiopropyl group.

Modification of the phosphate, ribose and the 2 and 8 positions on the purine ring of ATP resulted in potent antagonists. Replacement of the 6-amino group with either a hydrogen, hydroxyl or dialkylamino group resulted in a substantial drop in receptor affinity, whereas alkylamino substitution with $NHCH_2CH_2SMe$ resulted in an improved pharmacodynamic profile. An SAR study of substitution at the 6 position showed the receptor affinity in the order of $NHCH_2CH_2SMe > NH_2 > H > NEt_2 > OH$, with pIC_{50} values of 9.4 > 8.6 > 6.9 > 5.5 > 5.15, respectively.

The importance of the ribose sugar linking the adenine base to the acidic chain was shown when its replacement by alkyl groups of varying lengths led to a 600- to 4000-fold loss of affinity, while the importance of the full complement of ribose hydroxyl groups was shown by the 40- to 120-fold drop in affinity for the 2'-deoxy and 3'-deoxy analogs of FPL-67085 [162135]. Part of the activity of FPL-67085 resides in the dichloromethylenediphosphonate moiety, which is incorporated to prevent metabolism to the corresponding ADP analog with agonist activity at P2T-purinoceptors. Variations of this moiety have been incorporated into a range of P2T-purinoceptor antagonists [162174]. The most effective of these were 2-propylthio analogs, in which the β-γ-diphosphate portion of the acidic triphosphate chain of ATP was replaced by difluoromethylenediphosphonate (FPL-66099), dichloromethylenediphosphonate (FPL-67085) and dibromomethylenephosphonate (FPL-67121), which had K_B values of ≤ 2 nM for antagonism of ADP-induced human platelet aggregation *in vitro* [162174]. The full synthetic process for cangrelor and the formulation that has been used in clinical trials has not yet been published.

On further investigation, removal of the triphosphate side chain and modification of the ribose to a carbocycle and the purine to a triazolopyridine resulted in a potent and orally active $P2Y_{12}$ receptor antagonist (IC_{50} = 4 nM) [393813].

Pharmacology

Cangrelor has a pIC_{50} value of 9.3 at the platelet P2T receptor, is designed for intravenous infusion and has a rapid metabolic clearance [298703], [298980], [298982], [298983]. It has excellent selectivity over other P2 and P1 receptors [377418].

ADP-induced platelet aggregation is mediated via activation of the purinergic $P2Y_1$ receptor, which is coupled to calcium mobilization and initiates shape change and aggregation, while another P2 receptor (ie, P2T), which is coupled through Gi_2 and adenylyl cyclase, inhibition is responsible for the completion and amplification of the response [393814]. *In vitro* studies in Gaq-deficient mouse platelets have confirmed the inhibition of ADP-induced platelet aggregation by blocking the latter receptor [393814].

Shear-induced aggregation in heparinized blood was reduced by 54% with addition of 500 nM of the P2T antagonist and was further reduced by 29% with the combination of 500 nM P2T antagonist plus 100 μM of the $P2Y_1$ antagonist, A3P5P [350492]. Blockade of both ADP receptors, P2T and $P2Y_1$, is necessary for effective inhibition of platelet aggregation [381573]. One study established that ADP potentiates plasmin-induced platelet aggregation and cangrelor inhibits the P2T-mediated action of ADP without inhibiting the $P2Y_1$-mediated action of ADP [381556].

To assess the potential for undesirable antihemostatic effects, cangrelor was compared to the GPIIb/IIIa antagonist, lamifiban (F Hoffmann-La Roche), in anesthetized dogs. Dose-response relationships of cangrelor displayed a favorable 98-fold separation between the desired antithrombotic effect and the prolongation of bleeding time, in contrast to the significant prolongation of the bleeding time seen with effective antithrombotic doses of lamifiban. Consequently, the complete inhibition of platelet aggregation needed to give an antithrombotic effect was achieved at doses which extend bleeding time by > 2-fold [315723].

Cangrelor has also been evaluated for electrolytic injury coronary thrombosis in a dog model. Thrombosis was induced using electrolytic technique in 20 dogs. All the animals received either cangrelor (4 mg/kg/min iv) or saline for a total of 2 h with an iv bolus and continuous infusion of heparin. Platelet aggregation in response to ADP was reduced by half in the placebo group and approximately 20-fold in the cangrelor-treated group. The study reports that the administration of cangrelor in the canine model results in prolongation of reperfusion time and significant reduction in reocclusion and cyclic flow variation rate [381566].

The efficacy of cangrelor in the prevention of primary occlusive arterial thrombosis in a canine model was studied in 11 beagle dogs [393812]. The drug was infused at a rate of 4.0 μg/kg/min iv to six dogs and 0.9% saline to a control group of five dogs. This investigation proved that the selective inhibition of the platelet P2T receptor resulted in *ex vivo* inhibition of ADP-induced platelet aggregation.

Metabolism

No data are currently available.

Toxicity

In an *in vivo* study, there were no significant placebo- or drug-related changes in heart rate or arterial blood pressure [393812].

Clinical Development

Phase I

Results from phase I trials have demonstrated that a 100% block of platelet aggregation can be achieved by cangrelor with only a 1.5-fold increase in bleeding time, which

correlates well with previous data collected from the dog cyclic flow reduction model. Furthermore, bleeding returned to normal by only 30 min post iv administration. This profile compared favorably to that seen with GPIIb/IIIa antagonists, such as lamifiban (iv). No interactions between cangrelor and aspirin or heparin were observed [308718].

In healthy male and female human volunteers, cangrelor produced a dose-dependent inhibition of *ex vivo* ADP-induced platelet aggregation (APA). Reversal of inhibition of APA was rapid and complete within 20 min from the highest dose, and no rebound APA was reported. At doses that abolished APA, bleeding time of cangrelor increased by 3.2-fold in males and 2.9-fold in females. Plasma clearance was 50 l/h with low variability (14%) and a very short duration of action. The short half-life of approximately 2.6 min resulted in rapid attainment of steady-state concentrations in all subjects, while the compound showed dose linearity with no detectable pharmacokinetic sex differences [315723], [316436].

Results of a trial of cangrelor in comparison with clopidogrel in eight healthy volunteers were presented at the 41st Annual Meeting of the American Society of Hematology (New Orleans, USA) in December 1999. Cangrelor achieved 97% inhibition of 10 µM ADP on day 0, compared to 46% inhibition of 10 µM ADP for clopidogrel on day 11. Clopidogrel incompletely blocks the P2T receptors; functional receptors remained even after 11 days of treatment. P2T receptors are completely blocked by cangrelor, which fully antagonizes ADP-induced P2T receptor activation [350114].

Phase II

Phase IIa trials with an iv formulation determined the safety, tolerability, activity and doses of cangrelor for a phase IIb trial which began in late 1998.

Cangrelor was assessed for inhibition of platelet aggregation in 39 patients with acute coronary syndrome. The patients who received aspirin and heparin were also administered cangrelor (infusion rate 2 mg/kg/min or 4 mg/kg/min iv) as an adjunctive therapy. Cangrelor was well tolerated in all the patients with no major or minor bleeds. Steady state plasma levels and stable inhibition of platelet aggregation were achieved within 30 min of infusion [348657]. The mean plasma half-life of cangrelor was < 5 min.

Cangrelor was further evaluated for tolerance and safety in a double-blind, placebo-controlled, dose-response study conducted in patients undergoing percutaneous coronary intervention (PCI) [381572]. Preliminary results showed that the addition of cangrelor to heparin and aspirin during the PCI was tolerated to a dose of 4.0 mg/kg/min iv and not associated with any significant increase of major bleeding and major adverse cardiac events [381572].

Furthermore, a double-blind, randomized, placebo-controlled study was conducted in 94 patients with unstable angina/non-Q-wave myocardial infarction in Sweden at eight different centers to study the safety and tolerability of iv infusion of cangrelor [381562]. The drug was well tolerated hemodynamically and there were no significant changes in laboratory findings between the placebo and treated group. The incidence of minor bleeding events was slightly higher in patients receiving cangrelor. The study showed that cangrelor, as an adjunctive therapy to aspirin and low molecular weight heparin in acute coronary syndrome, was safe and well tolerated [381562].

Clinical findings have confirmed that cangrelor is a more effective inhibitor of ADP-induced platelet aggregation than a prodrug, clopidogrel [381585].

Side Effects and Contraindications

Cangrelor was tolerated in volunteers with only minor increases in petechial or brushing reaction [316436]. The risk of persistent hemorrhage following administration of a P2T antagonist is stated to be much less likely than with GPIIb/IIIa antagonists, such as lamifiban [315723].

Current Opinion

There is currently a need for more effective antithrombotic agents for the prevention of arterial coronary syndromes. Antiplatelet therapies include cyclooxygenase inhibitors (aspirin), thromboxane receptor antagonists, prostacyclin receptor agonists, GPIIb/IIIa receptor antagonists (antibody-derived abciximab (Centocor), non-peptides such as tirofiban (Merck & Co), lamifiban and the venom-derived eptifibatide (COR Therapeutics)), P2T-purinoceptor specific thienopyridines with a poorly-defined mechanism of action (clopidogrel (Sanofi-Synthélabo), ticlopidine), and thrombin receptor antagonists (heparin, warfarin, hirudin, desirudin (Novartis), bivalrirudin (Biogen)). To date, significant benefit has been achieved using aspirin as an antithrombotic agent. The advantages are that it is well-established, relatively safe to administer and cheap. However, aspirin has limited clinical efficacy as it interferes mechanistically only with thromboxane-induced platelet aggregation [338622], while other compounds, such as ticlopidine, exhibit unwanted side effect profiles. Moreover, they are relatively poor inhibitors of platelet aggregation, inhibiting only one of the many pathways involved in platelet activation [334640]. The competition to develop more effective antithrombotic agents like GPIIb/IIIa receptor antagonists resulted in complications such as major bleeding, necessitating blood transfusion [235864].

There is a therapeutic need for a potent intravenous antithrombotic agent for use in episodes of acute arterial thrombosis. In such circumstances, the highly polar nature of ATP analogs could be advantageous, and the pharmacodynamic and functional pharmacokinetic profiles of cangrelor indicate that it may be used for the treatment of acute thrombotic conditions. Cangrelor is being developed to address what AstraZeneca defines as an unmet need for intravenous antithrombotic agents to treat acute arterial coronary syndromes such as unstable angina, and in the setting of percutaneous transluminal coronary artery revascularization [315723]. The current analysis based on the reported literature suggests that the adverse effects related to the risk of persistent hemorrhage following administration of a P2T receptor

antagonist are likely to be much lower than with GPIIb/IIIa antagonists [315723]. The substantial separation of the antithrombic activity from effects of bleeding time constitutes a major advantage for P2T antagonists in the modulation of platelet aggregation. The 'rapid-on' and 'rapid-off' kinetics of cangrelor may provide a convenient means of maintaining control of platelet function under clinical conditions.

A significant role for P2T-purinoceptor-mediated actions of endogenous ADP in platelet thrombus formation was demonstrated by researchers at Fisons using animal models of thrombosis, but whether ADP is actually an important participant in acute thrombogenesis in humans awaits the results of pivotal clinical trials. The literature suggests that the combinations of P2T and $P2Y_1$ antagonists are effective as an antithrombotic agents.

Cangrelor may also have significant antagonist effects on other as yet unidentified purinoceptors with a similar structural conformation to the target P2T-purinoceptor, as well as significant agonist activities at P2X- and other subtypes of P2Y-purinoceptors. The success of the compound as an antithrombotic agent will also depend on its efficacy and safety in larger trials, but nonetheless, cangrelor shows promise as an ultra short-acting antiplatelet compound for the prevention and treatment of acute thrombotic events.

Development history

Study Type	Country	Status	Indication	Date	Reference
AstraZeneca plc	Sweden	C2	Angina	01-FEB-99	314472
AstraZeneca plc	Sweden	C2	Thrombosis	01-FEB-99	314472
AstraZeneca plc	UK	C2	Angina	01-FEB-99	314472
AstraZeneca plc	UK	C2	Myocardial infarction	01-FEB-99	314472

Literature classifications

Chemistry

Study Type	Result	Reference
Synthesis and SAR	Modification of the phosphate, ribose and the 2 and 8 positions on the purine ring system of ATP, resulted in potent antagonists. Replacement of 6-amino group with either a hydrogen, hydroxyl or dialkylamino group resulted in a substantial drop in receptor affinity, whereas alkylamino substitution with $NHCH_2CH_2SMe$ resulted in an improved pharmacodynamic profile. An SAR study of substitution at the 6 position showed the receptor affinity in the order of $NHCH_2CH_2SMe > NH_2 > H > NEt_2 > OH$, with pIC_{50} values of 9.4 > 8.6 > 6.9 > 5.5 > 5.15.	298983
Structure	Cangrelor is an analog of ATP with a 3,3,3-trifluoropropylthio substituent at C(2), an *N*-methylthioethyl substituents on the purine (adenine) base and a dichloromethylene group replacing the β-γ linking oxygen in the acidic triphosphate chain.	315723
Synthesis and SAR	The ribose sugar linking the adenine base to the acidic chain was shown to be important by replacement with alkyl groups of varying lengths, leading to a 600- to 4000-fold loss of affinity, while the importance of the full complement of ribose hydroxyl groups was shown by the 40- to 120-fold drop in affinity for the 2'-deoxy and 3'-deoxy analogs of FPL-67085.	162135

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Hemostatic side effects; comparison with the GPIIb/IIIa antagonist, lamifiban.	Anesthetized dogs.	Dose-response relationships of cangrelor displayed a favorable 98-fold separation between the desired antithrombotic effect and the prolongation of bleeding time, in contrast to the significant prolongation of the bleeding time seen with effective antithrombotic doses of lamifiban. Complete inhibition of platelet aggregation is achieved at doses which extend bleeding time by < 2-fold.	315723
In vivo	Platelet aggregation.	Electrolytic injury coronary thrombosis in dog model. Animals received either cangrelor (4 mg/kg/min iv) or saline for a total of 2 h with an iv bolus and continuous infusion of heparin.	Platelet aggregation in response to ADP was reduced by half in the placebo group and approximately 20-fold in the cangrelor-treated group.	381566

Clinical

Effect Studied	Experimental Model	Result	
Pharmacokinetics.	Phase I in healthy male and female volunteers.	Plasma clearance was 50 l/h with low variability (14%), and a very short duration of action. The short half-life of ~ 2.6 min resulted in rapid attainment of steady-state concentrations in all subjects, while the compound showed dose linearity with no detectable pharmacokinetic sex differences.	315723 316436
Platelet aggregation and bleeding.	Phase I trial.	Complete block of platelet aggregation can be achieved by cangrelor with only a 1.5-fold increase in bleeding time. Furthermore, bleeding returned to normal 30 min post iv administration. This profile compared favorably to that seen with lamifiban. No interactions between cangrelor and aspirin or heparin were observed.	308718

Associated patent

Title N-alkyl-2-substituted ATP analogues.

Assignee Fisons plc

Publication WO-09418216 18-AUG-94

Priority GB-00025712 16-DEC-93

Inventors Ingall A, Cage P, Kindon N.

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